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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02013693.3

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Nasal compositions

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Nasal Compositions

The present invention relates to pharmaceutical compositions intended for nasal administration. More specifically, it concerns nasal formulations with improved moisturizing properties. What is in particular strived for is nasal compositions that further can be formulated "preservative-free", which means that they do not contain any special preservative and nevertheless fulfill all requirements with respect to microbiological stability, i.e. that germs are killed efficaciously over the whole shelf life of the nasal product concerned.

The nasal administration of active substances is a widely used method of treatment. Active substances that come into consideration are, for example, vasoconstrictors, such as xylometazoline, or antiallergic agents, such as H_1 receptor antagonists, e.g. dimethindene maleate. Another group of possible active substances is e.g. corticosteroids, such as beclomethasone or fluticasone.

The indications in which a certain nasally administered drug is to be applied are known in the art. For example, vasoconstrictors are e.g. used as nasal decongestants for alleviating the typical symptoms of common cold, like running nose, obstructed nose etc., or in rhinitis or sinusitis. Antiallergic agents and corticosteroids are e.g. used in antiallergic conditions, e.g. hay fever, or in anti-asthmatic or anti-inflammatory conditions.

Nasal administration of active substances can be accomplished e.g. bei nasal formulations in liquid form, such as drops, solutions, sprays (nebulizers) or metered-dose sprays, or in semi-solid form, such as gels or creams.

However, upon administration of nasal formulations often the patients are suffering from side effects like burning, dryness, stinging of the nasal mucosa or sneezing. One of the main reasons for this is that the nasal mucosa is not sufficiently moisturized and/or is not kept moisturized long enough after administration.

The present invention addresses these problems and provides nasal formulations that exhibit excellent moisturizing properties. Moreover, they can be formulated "preservative-

free". Said goals have been achieved by selecting a specific beneficial mixture of ingredients for said nasal formulations.

Although the focus in the beginning was primarily on obtaining preservative-free formulations, in the course of experimentations it has been found that said formulations are also very suitable when combined with a preservative. Thus, it is justified to define preservatives as an optional component of the compositions of the invention, with the compositions without preservative being preferred.

The invention therefore relates to a nasal pharmaceutical composition that comprises
(a) at least one active substance suitable for nasal administration,
(b) a mucopolysaccharide, and
(c) propylene glycol.

Active substances suitable for nasal administration (a) are e.g. vasoconstrictors, e.g. xylometazoline, e.g. xylometazoline hydrochloride; indanazoline, metizoline; naphazoline, e.g. naphazoline hydrochloride; fenoxazoline, e.g. fenoxazoline hydrochloride; oxymetazoline, e.g. oxymetazoline hydrochloride; tetrahydrozoline, tramazoline, tymazoline; phenylephrine, e.g. phenylephrine hydrochloride; ephedrine, e.g. d-pseudoephedrine hydrochloride; or epinephrine; or antiallergic agents, such as H_1 receptor antagonists, e.g. dimethindene or a nasally acceptable salt thereof, e.g. dimethindene maleate; acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate, pyrilamine, tripelennamine, cetirizine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine or terfenadine. Examples for corticosteroids are e.g. beclomethasone, e.g. beclomethasone dipropionate, or fluticasone, e.g. fluticasone propionate. All active substances which are capable of salt formation may be present either in free form or in the form of a nasally acceptable salt. Also mixtures of more than one active substance come into consideration, e.g. a combination of a vasoconstrictor and an antiallergic agent, such as xylometazoline plus dimethindene or phenylephrine plus dimethindene, or a combination of a vasoconstrictor and a corticosteroid, such as xylometazoline plus beclomethasone.

In one embodiment of the invention, the active substances used are vasoconstrictors, e.g. xylometazoline, naphazoline, fenoxazoline, oxymetazoline, tetrahydrozoline, tramazoline, phenylephrine, ephedrine or epinephrine, or any nasally acceptable salt thereof. In particular preferred are xylometazoline and oxymetazoline, especially xylometazoline, and nasally acceptable salts thereof.

The concentration of the active substances is typically chosen so that a pharmaceutically, i.e. nasally, effective dose thereof can be administered easily, e.g. by a certain number of drops or by spraying.

For example, if a vasoconstrictor is used as active substance (a), it is e.g. present in an amount of from 0.005 up to 0.5%, preferably of from 0.01 up to 0.3%, and in particular of from 0.025 up to 0.2% (w/w) of the total composition.

The term mucopolysaccharide (b) comprises glycosaminoglycans, e.g. heparinoids, e.g. chondroitin, dermatan and nasally acceptable salts of any of said compounds, especially chondroitin sulfate and dermatan sulfate; hyaluronic acid, or a nasally acceptable salt thereof, e.g. sodium hyaluronate; keratan, or a nasally acceptable salt thereof, e.g. keratan sulfate; heparin, or a nasally acceptable salt thereof, e.g. heparin sulfate; or acemannan.

Preferred are chondroitin, or a nasally acceptable salt thereof, e.g. chondroitin sulfate, hyaluronic acid, or a nasally acceptable salt thereof, e.g. sodium hyaluronate; and dermatan, or a nasally acceptable salt thereof, e.g. dermatan sulfate. Especially preferred is chondroitin sulfate.

The component (b) is e.g. present in an amount of from 0.01 up to 5%, preferably of from 0.02 up to 3%, and in particular of from 0.05 up to 2%, (w/w) of the total composition.

Depending on what type of nasal composition is intended (liquid, viscous liquid, gel) the amount of (b) must be adjusted accordingly. Concretely, the more viscous the composition is to be, the more of (b) has typically to be included. The amount of (b) further depends on the kind of mucopolysaccharide (b) used.

Preferred amounts of chondroitin, or a nasally acceptable salt thereof, to be used are of from 0.1 up to 5%, in particular of from 0.25 up to 2%. Preferred amounts of hyaluronic acid, or a nasally acceptable salt thereof, to be used are of from 0.02 up to 1%, in particular of from 0.05 up to 0.5%.

In the nasal compositions of the invention, propylene glycol (c) is typically present in an amount of 0.5 up to 10%, preferably 1 up to 5%, more preferably 1.5 up to 3%, and in particular 1.7 up to 2.5%.

Optionally, the nasal compositions of the invention may further include a nasally acceptable film-forming agent. By adding it, the moisturizing and soothing effects of the compositions of the invention may be reinforced, namely by restricting the loss of water and thus longer maintaining a good level of hydration of the nasal mucosa. That way the comfort sensation of the patient may further be improved. Preferred are water soluble or swellable cellulose materials, e.g. hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose or sodium carboxymethyl cellulose, and polyvinylpyrrolidone (povidone) or cross-linked polyvinylpyrrolidone (crospovidone).

Optionally, the nasal compositions of the invention may further include a nasally acceptable preservative. The latter are well known in the art. Examples are benzalkonium chloride, benzoxonium chloride, benzododecinium bromide, benzethonium chloride, cetylpyridinium chloride, cetrimide, benzoic acid and esters thereof, e.g. C1-C7-alkyl esters of 4-hydroxy-benzoic acid, such as methyl para-hydroxybenzoate, and chlorhexidine or nasally acceptable salts thereof, e.g. chlorhexidine digluconate, chlorhexidine acetate or chlorhexidine chloride. If present, they are used in usual amounts, e.g. benzalkonium chloride and benzoxonium chloride typically in amounts of from 0.005 up to 0.03%, in particular 0.01-0.02 %, (w/w) of the total composition.

In a specific embodiment of the invention, those nasal compositions that further include a nasally acceptable preservative do not include any unsubstituted or hydroxy-substituted C1-C21-alkyl-beta-cyclodextrin.

In another embodiment of the invention, the nasal compositions of the invention are devoid of an additional nasally acceptable preservative.

Optionally, the nasal compositions of the invention may further include an essential oil of a plant, e.g. lavender, rosemary or tea tree, especially in the form of a water-soluble extract.

Typically, there is also present a vehicle in the nasal compositions of the invention. The vehicle is usually present in an amount of at least 90% - preferably at least 92%, especially at least 94% and in particular at least 96% - (w/w) of the total composition. The vehicle is preferably water but can also be e.g. a mixture of water with another nasally acceptable solvent that is miscible with water, e.g. glycerol.

Moreover, the nasal compositions of the invention may contain usual nasally acceptable excipients that are known in the art and include e.g. buffering agents, chelating agents and/or isotonicity regulators.

The nasal compositions of the invention show e.g. excellent moisturizing and soothing properties, they cause a sensation of comfort, and therefore test persons excellently accept them. A significant reduction of symptoms like burning, dryness, stinging of the nasal mucosa or sneezing is found upon administration of the compositions.

The beneficial properties of the compositions of the invention can be demonstrated e.g. by the following tests: For example, the moisturizing properties can be shown in hair humidity measurements by transient thermal transfer, e.g. in the Hydrascan® device provided by Laboratoire Demscan, France. Or the level of hydration of the nasal mucosa can also be demonstrated e.g. by showing the distribution of tritiated water within a mucosa model, e.g. pig trachea. In microbiological "challenge" tests, e.g. over 6 weeks, the compositions of the invention – including those comprising no special preservative – remain free of germs.

Moreover, consumer research studies show that the nasal compositions of the invention, surprisingly, are perceived more moisturizing and less drying than other commercially available compositions.

The nasal compositions of the invention can be manufactured in a manner known per se, for example by conventional mixing and dissolution methods in aqueous vehicles.

The following examples illustrate the invention.

Example 1: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride

Ingredients	Amount (kg/100kg)
Xylometazoline hydrochloride	0.10
Chondroitin sulfate	1.0
Propylene glycol	2.0
Sodium dihydrogen phosphate dihydrate	0.16
Disodium phosphate dodecahydrate	0.085
Disodium edetate	0.050
Purified water	ad 100.0

Manufacturing method (for a batch of 100 liters): Introduce 88.605 kg of purified water into a dissolutor, add chondroitin sulfate under stirring and continue to stir until dissolution will be complete. Add sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, disodium edetate and stir until complete dissolution. Add propylene glycol under stirring and xylometazoline hydrochloride to the solution, continue to stir until dissolution will be complete. Rinse with 8.0 kg of purified water. Filter solution through a 0.22 micrometer filter.

Example 1a: Nasal sprays containing 0.05 % (w/w) of xylometazoline hydrochloride are manufactured analogously to Example 1 by using 0.05 kg of xylometazoline hydrochloride (instead of 0.10 kg) and starting with 88.655 kg of purified water (instead of 88.605 kg).

Example 2: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride (with film-forming agent)

Ingredients	Amount (kg/100kg)
Xylometazoline hydrochloride	0.10
Chondroitin sulfate	1.0
Propylene glycol	2.0
Sodium dihydrogen phosphate dihydrate	0.16
Disodium phosphate dodecahydrate	0.085

Disodium edetate	0.05
Hydroxypropyl methyl cellulose	0.10
Purified water	ad 100.0

Manufacturing method (for a batch of 100 liters): Introduce 88.505 kg of purified water into a dissolutor, disperse hydroxypropyl methyl cellulose under stirring, after dissolution continue to stir for 30 minutes. Add chondroitin sulfate under stirring and continue to stir until dissolution will be complete. Add sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, disodium edetate and stir until complete dissolution. Add propylene glycol under stirring and xylometazoline hydrochloride to the solution. Continue to stir until dissolution of the active substance will be complete. Rince with 8.0 kg of purified water. Filter solution through a 0.22 micrometer filter.

Example 2a: Nasal sprays containing 0.05% (w/w) of xylometazoline hydrochloride (with film-forming agent) are manufactured analogously to Example 1 by using 0.05 kg of xylometazoline hydrochloride (instead of 0.10 kg) and starting with 88.555 kg of purified water (instead of 88.505 kg).

Example 3: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride

Ingredients	Amount (kg/100kg)
Xylometazoline hydrochloride	0.10
Sodium hyaluronate	0.10
Propylene glycol	2.0
Sodium dihydrogen phosphate dihydrate	0.16
Disodium phosphate dodecahydrate	0.085
Disodium edetate	0.05
Purified water	ad 100.00

Manufacturing method: The nasal drops are manufactured in a manner analogous to Example 1.

Example 4: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride (with lavender essential oil)

Ingredients	Amount (kg/100kg)
Xylometazoline hydrochloride	0.10
Chondroitin sulfate	1.0
Propylene glycol	2.0
Sodium dihydrogen phosphate dihydrate	0.16
Disodium phosphate dodecahydrate	0.085
Disodium edetate	0.05
Hydroxypropyl methyl cellulose	0.10
Lavender oil	0.10
Cremophor RH40 (= PEG-40 hydrogenated castor oil)	0.50
Purified water	ad 100.0

Manufacturing method (for a batch of 100 liters): Introduce 87.905 kg of purified water into a dissolutor, disperse methylhydroxypropylcellulose under stirring, after dissolution continue to stir for 30 minutes. Add chondroitin sulfate under stirring and continue to stir until dissolution will be complete. Add sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, disodium edetate and stir until complete dissolution. Add propylene glycol under stirring and xylometazoline hydrochloride to the solution. Continue to stir until dissolution of the active substance will be complete. Introduce in a small stainless steel container the Cremophor RH40 add Lavender essential oil, stir until a clear solution is obtained. Then slowly add 8.0 kg of purified water. Introduce said latter solution into the former one. Filter combined solution through a 0.22 micrometer filter.

Example 4a: Nasal drops containing 0.1% (w/w) of xylometazoline hydrochloride (with tea tree essential oil) are manufactured analogously to Example 4 by using 0.10 kg of tea tree oil (instead of 0.10 kg of lavender oil).

Example 5: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride (with preservative chlorhexidine digluconate)

Ingredients	Amount (kg/100kg)
Xylometazoline hydrochloride	0.10
Chondroitin sulfate	1.0

Propylene glycol	2.0
Disodium edetate	0.05
Hydroxypropyl methyl cellulose	0.10
Citric acid	0.10
Disodium phosphate anhydous	0.22
Chlorhexidine digluconate	0.02
Purified water	ad 100.0

Manufacturing method (for a batch of 100 liters): Introduce 96.41 kg of purified water into a dissolutor, disperse hydroxypropyl methyl cellulose under stirring, after dissolution continue to stir for 30 minutes. Add disodium phospate anhydrous and citric acid under stirring until dissolution and then add chondroitin sulfate, continue to stir until dissolution will be complete. Maintain stirring for further 15 minutes. Dissolve disodium edetate, propylene glycol and xylometazoline hydrochloride in the solution. Continue to stir until dissolution of the active substance will be complete. Filter solution through a 0.45 micrometer filter.

Example 5a: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride (with preservative cetylpyridinium chloride) are manufactured analogously to Example 5 by using 0.02 kg of cetylpyridinium chloride (instead of 0.02 kg of chlorhexidine digluconate).

Example 5b: Nasal drops containing 0.1% (w/w) of xylometazoline hydrochloride (with preservative benzoxonium chloride) are manufactured analogously to Example 5 by using 0.02 kg of benzoxonium chloride (instead of 0.02 kg of chlorhexidine digluconate).

Example 5c: Nasal drops containing 0.1% (w/w) of xylometazoline hydrochloride (with preservative benzalkonium chloride) are manufactured analogously to Example 5 by using 0.02 kg of benzalkonium chloride (instead of 0.02 kg of chlorhexidine digluconate).

Example 6: Nasal drops containing 0.1% (w/w) of Xylometazoline hydrochloride (with preservative methyl 4-hydroxybenzoate)

Ingredients	Amount (kg/100kg)
Xylometazoline hydrochloride	0.10
Chondroitin sulfate	1.0

Propylene glycol	2.0
Sodium dihydrogen phosphate dihydrate	0.16
Disodium phosphate dodecahydrate	0.085
Disodium edetate	0.05
Hydroxypropyl methyl cellulose	0.10
Methyl 4-hydroxybenzoate	0.15
Purified water	ad 100.00

Manufacturing method (for a batch of 100 liters): Into a dissolutor introduce and heat at 85°C 96.355 kg of purified water, add methyl 4-hydroxybenzoate, maintain under stirring at this temperature for about 15 minutes until complete dissolution. Cool down to 75°C and add sodium dihydrogen phosphate dihydrate and disodium phosphate dodecahydrate. Continue to cool down to 35°C, then disperse hydroxypropyl methyl cellulose under stirring, and - after dissolution - continue to stir for 30 minutes. Add chondroitin sulfate, continue to stir until dissolution will be complete. Maintain the stirring for further 15 minutes. Dissolve disodium edetate, propylene glycol and xylometazoline hydrochloride in the solution. Continue to stir until dissolution of the active substance will be complete. Filter solution through a 0.45 micrometer filter.

Example 7: Nasal drops containing 0.05% (w/w) of oxymetazoline hydrochloride are manufactured in a manner analogous to Example 1a by using 0.05 kg of oxymetazoline hydrochloride (instead of 0.05 kg of xylometazoline hydrochloride).

Claims

1. A nasal pharmaceutical composition which comprises
(a) at least one active substance suitable for nasal administration,
(b) a mucopolysaccharide, and
(c) propylene glycol.

2. A composition according to claim 1, wherein the active substance (a) is selected from the group consisting of vasoconstrictors and antiallergic agents.

3. A composition according to claim 1, wherein the active substance (a) is selected from the group of vasoconstrictors consisting of xylometazoline, naphazoline, fenoxazoline, oxymetazoline, tetrahydrozoline, tramazoline, phenylephrine, ephedrine, epinephrine, and nasally acceptable salts of any of these compounds.

4. A composition according to claim 1, wherein the active substance (a) is xylometazoline or a nasally acceptable salt thereof.

5. A composition according to any one of claims 1-4, wherein the mucopolysaccharide (b) is selected from the group consisting of chondroitin, hyaluronic acid, dermatan, keratan, heparin, acemannan, and nasally acceptable salts of any of said compounds.

6. A composition according to any one of claims 1-5, wherein the mucopolysaccharide (b) is chondroitin sulfate.

7. A composition according to any one of claims 1-6, wherein the propylene glycol (c) is present in an amount of from 1 up to 5 % (w/w) of the total composition.

8. A composition according to any one of claims 1-7, which includes a vehicle and wherein said vehicle is water.

9. A composition according to any one of claims 1-8, which in addition includes a nasally acceptable film-forming agent.

10. A composition according to any one of claims 1-9, which in addition includes an essential oil of a plant.

11. A composition according to any one of claims 1-10, which in addition includes a nasally acceptable preservative.

12. A composition according to claim 11, which does not include any unsubstituted or hydroxy-substituted C1-C21-alkyl-beta-cyclodextrin.

13. A composition according to any one of claims 1-10, which is devoid of an additional nasally acceptable preservative.

14. A composition according to any one of claims 1-13, which is in the form of drops, a solution, a spray or a metered-dose spray.

Nasal Compositions

Abstract of the Disclosure

The invention relates to pharmaceutical compositions adapted to nasal administration. The nasal formulations of the invention are characterized inter alia by having excellent moisturizing properties and not requiring a preservative.